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PORTNER, VIRGINIA ALLEN

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/611,419	Applicant(s) Smith et al
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 13, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *39-86* is/are pending in the application.

4a) Of the above, claim(s) *43, 52, 57-81, 83, and 84* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *39-42, 44-51, 53-56, 82, 85, and 86* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *39-86* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *1*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-38 have been canceled.

Claims 39-86 are new pending claims.

Interview Summary

1. In light of a telephone interview with Ms. Rochelle Seide, Registration number 32,300, on September 10, 2001, the election made August 7, 2002 was clarified to be the combination of SEQ ID Nos 1, 3 and 5, and not to be all of the sequences that were set forth as being distinct, of Group I. A first action on the merits is set forth below.

Priority

Please Note: The elected SEQ ID Nos 1, 3 and 5 do not evidence 100% sequence identity with the sequences set forth the in parent application 08/123, 975. Original descriptive support in the parent application, 08/123, 975 was not found for SEQ ID Nos 1,3 and 5, nor the elected invention of the combination of SEQ ID Nos 1, 3 and 5. The instantly claimed invention is therefore afforded the priority date of May 12, 1999 (provision application) which evidences original descriptive support for each of these sequences.

Election/Restriction

2. In light of Applicant's amendment of claim 82 to only depend from claim 39, the claims of Group VI, specifically claims 82, 85 and 86, are herein rejoined with Group I as being drawn to the same invention.

3. Applicant's election with traverse of Group I, species SEQ ID Nos 1,3 and 5 (Claims 39-42, 44-51, 53-56, 82, 85 and 86 (species directed to carboxy-terminal), drawn to a nucleic acid molecule comprising a sequence for the (carboxy) C-terminal of the heavy chain of botulinum

neurotoxin, a host cell comprising the nucleic acid sequence and a method of using the nucleic acid to express a polypeptide through culturing the recombinant host cell, classified in class 514, subclass 44), in Paper No. 11 is acknowledged.

The traversal is on the ground(s) that " Groups I and III relate to domains of single botulinum neurotoxin molecules which can be used separately or in combination. Therefore, examination of these groups does not pose an undue search burden. Applicant's further assert that the restriction of Groups II, IV and V is improper since Group V is generic to Groups II and IV." These arguments have been fully considered but are not found to be persuasive for the reasons below.

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1)independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example, as product and method of use, but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.1). In the instant situation, the inventions of Groups I-VI are drawn to distinct inventions which are related as separate products capable of separate functions, specifically the N-terminal of the Heavy chain is associated with membrane translocation, the C-terminal of the Heavy chain is associated with neuronal receptor binding and the light chain evidences enzymatic activity. Restrictions between the inventions is deemed to be proper for the reason previously set forth.

In regard to burden of search and examination, MPEP 803 states that a burden can be shown if the examiner shows either separate classification, different field of search or separate status in the art. In the instant case a burden has been established in showing that the inventions

of Groups I-VI are classified separately necessitating different searches of issued US Patents . However, classification of subject matter is merely one indication of the burdensome nature of search. The literature search, particularly relevant in this art, is not co-extensive, because for example nucleic acid molecules evidence a different structure, chemical function and biological effect as compared with immunogenic proteins or epitopes. Additionally, it is submitted that the inventions of Groups I-VI have acquired a separate status in the art. Clearly different searches and issues are involved in the examination of each Group. For these reasons the restriction requirement is deemed to be proper and is therefore made Final.

4. Claims 43 (non-elected sequences), 52, 57-79, 80-81 and 83-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups II-VI, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Sequence Letter

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

6. APPLICANT IS GIVEN the time period set for THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

7. At the following locations SEQ ID Nos need to be inserted or assigned to the sequences:

a. Figure 8 (two sequences)

b. Page 12, lines 15-31;

c. Page 13, lines 8-24;

d. Page 36, lines 18-26;

e. Page 37, lines 1-27;

f. Page 38, lines 8-16 and lines 26-32 through page 39, lines 1-21.

Drawings

8. The drawings are objected to because the Brief Description of the drawings does not refer to the multiple frames shown in each figure, specifically Figure 1, A&B etc . Amendment of the Brief Description of the Drawings to refer to the frames set forth in each figure where more than one frame is shown is requested (see page 9 and 10 of instant specification and the drawings).

Information Disclosure Statement

9. The information disclosure statement (PTO-1449) filed July 6, 2000 has been considered prior to first action.

Claim Rejections - 35 U.S.C. § 101

10. 35 U.S.C. 101 reads as follows:

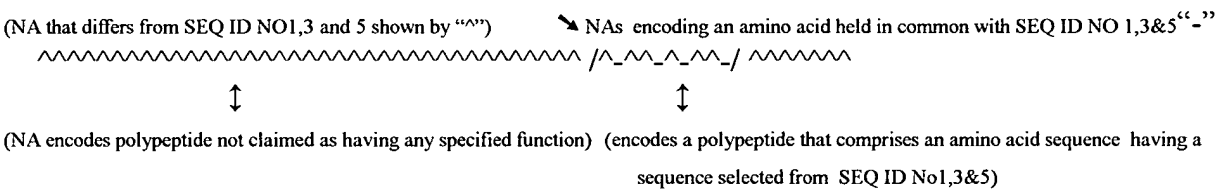
> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 39-42, 45-47, 55-56 are not directed to isolated and purified nucleic acid molecules and therefore read on a product of nature; the claimed invention is directed to non-statutory subject matter.

12. Claims 48-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are drawn to a method of making a polypeptide that comprises a portion of the carboxy terminal of a botulinum neurotoxin, this portion being any portion which is not required to have any specific function. The method of making a polypeptide with no required biological function, need only share a portion of a sequence, of any length, the portion being encoded by any of SEQ ID NO 1, 3 and 5.

Reference Sequence:
SEQ ID NO. 1, 3 and 5: ----------
What is claimed:



Absent factual evidence, a percentage sequence similarity of less than 100 % is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of a similar known biomolecule. It is known for nucleic acids, as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence identity or similarity results in an unpredictable product and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement.

Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over

biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al.[BioEssays, Volume 18, Number 12, pages 973-981{1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; and Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)].

The asserted utility of an isolated nucleic acid fragment that encodes a polypeptide that does not have specified biological activity is considered not to evidence a "specific" utility, i.e. they are not specific to the disclosed and claimed compounds properties of claim 39. As such, further research would be required to identify or reasonably confirm a "real world" context of use. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved would be required.

Therefore, the specification does not fairly disclose a substantial utility for the claimed embodiments. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Therefore, the claimed invention of isolated nucleic acid fragment encoding a polypeptide that comprises any amino acid sequence of SEQ ID NO 8, is not supported by a specific asserted utility for the reasons set forth above.

Applicant is directed to the Revised Interim Utility Guidelines, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999. In keeping with the revised utility guidelines and corresponding training materials (available on the PTO Website), none of the disclosed uses is a specific and/or substantial use.

13. Claims 48-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 U.S.C. § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 39-42, 44-51, 55-56, 82, 85-86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a full, clear, concise way, and exact terms or in sufficient detail as to reasonably convey to one skilled in the relevant art that can reasonably conclude that applicant had possession of the claimed invention at the time of filing. *This is a written description rejection.*

The claimed invention is directed to a nucleic acid that comprises a nucleic acid, and a nucleic acid that comprises a nucleic acid that encodes a polypeptide having an amino acid sequence encoded by a sequence selected from SEQ ID No 1, 3 and/or 5, the amino acid sequence being any amino acid sequence and is a polypeptide without any specific biological function .

Applicant has disclosed nucleotide sequences of SEQ ID NO 1,3 and 5 which encode a toxin sequence within the claimed genus of nucleic acids, which includes nucleic acids that comprise fragments of these sequence of any size. Within the scope of the now claimed invention are variant nucleic acids set forth through the recitation of the phrase "a nucleic acid comprising a nucleic acid sequence" which encompasses variant nucleic acid sequences with unspecified substitutions, alterations, deletions, but are not so claimed to evidence any recited biological activity. The claimed nucleic acids encompass gene sequences, corresponding sequences from other species, mutated sequences, allelic variants, splice variants, and any nucleic acid fragment that encodes any nucleic acid sequence that at least a portion of SEQ ID Nos, 1,3 and 5 held in common. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claims.

SEQ ID Nos 1, 3 and 5 are three species of nucleic acid sequences which are insufficient written description to support the claimed genus even though SEQ ID Nos 1, 3 and 5 meet the written description requirement under 35 U.S.C. 112, first paragraph. Description of a single species is insufficient to support a highly variable genus. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art

that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:1, 3 and 5, the skilled artisan cannot envision the detailed chemical structure of the encompassed isolated nucleic acid comprise a nucleic acid fragment of 1, 3 and 5 , regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 8 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 continued:

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for

obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only SEQ ID NOs: 1, 3 and 5, that encode an amino acid sequence with the biological function of a Hc fragment that binds to a neuron receptor but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

17. Claims 39-42, 44-51, 55-56, 82, 85-86 are rejected under 35 U.S.C. 112, first paragraph (New Matter), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 42 recites the phrase "SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5, or combinations thereof." The elected invention is "combinations thereof".

Upon consideration of the disclosure of the instant specification for a nucleic acid that is a combination of SEQ ID No 1, 3 and 5, no original descriptive support was found. The originally submitted claims do not provide support for the newly submitted claim limitations. A nucleic acid that is the combination of SEQ ID No 1, 3 and 5 does not evidence original descriptive support in the instant specification. All of the claims are being read to include the claim limitations of claim 42, which depends from independent claim 39. All of the claims recite New Matter. Applicant is requested to point out wherein the specification original descriptive support is provided for the elected embodiment recited in the amended claims. In response to this Office Action the New Matter should be canceled.

18. Claim 54 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 54 utilizes a recombinant organism that is capable of expressing a botulinum neurotoxin. The recombinant organism does not comprise the coding sequence for a botulinum neurotoxin, and

the organism is not so claimed to be a Clostridium botulinum recombinant strain. Claim 54 which is directed to a method is not enabled for the preparation of an immunogenic composition that comprises a botulinum neurotoxin as the recombinant organism does not produce or express or comprise a coding sequence for a botulinum neurotoxin.

19. Claims 39-42, 44-51, 53-56, 82, 85 and 86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39-42,44-51, 53-56, 82, 85 and 86 recite non-elected inventions; the elected invention is not distinctly claimed.

Claim 39 recites the phrase " encodes the carboxyl-terminal portion". What is the claimed nucleic acid that comprises this portion? What does the claimed nucleic acid encode or what will it hybridize to if it only comprises a portion? Clarification of the invention is requested.

Claim 39 recites the phrase "is capable of". The phrase does not define the presence of any specific structural components in the claimed nucleic acid and is not being viewed as defining any claim limitations of patentable weight. If what is intended are specific structural changes, the invention is not distinctly claimed.

Claim 40 depends from claim 39 and recites the phrase "the gram negative bacteria is Escherichia coli". As the claimed invention is directed to a nucleic acid from Clostridium (botulinum), the redefinition of the nucleic acid to be from E.coli is confusing in light of the claimed product is not a recombinant host cell that comprises a heterologous nucleic acid. Claim 40 should depend from claim 82.

Claim 41 depends from claim 39 and recites the phrase "the yeast is Pichia pastoris". As the claimed invention is directed to a nucleic acid from Clostridium (botulinum), the redefinition of the nucleic acid to be from Pichia pastoris is confusing in light of the claimed product is not a

recombinant host cell that comprises a heterologous nucleic acid. Claim 41 should depend from claim 82.

Claim 44 depends from claim 39 and recites the phrase "wherein the nucleic acid is a synthetic nucleic acid." In light of claim 39 not being an isolated and purified nucleic acid, or a recombinant nucleic acid, how can the nucleic acid of claim 44 define claim 39 to be synthetic?

Claims 45 and 46 should recite the phrase --further comprises--, as the nucleic acid of claim 39 only encodes for a portion of the heavy chain carboxy-terminal. No expression control sequences are claimed in claim 39 from which 45 and 46 depend.

Claim 48 defines mammalian cells as organisms. Mammalian cells are not microorganisms, but cells. The invention is not distinctly claimed.

Claim 48 recites the step of "transfecting an organism with the nucleic acid of claim 39". The nucleic acid of claim 39 is not limited to encoding a botulinum neurotoxin, but is a nucleic acid that comprises a nucleic acid sequence that encodes the carboxyl-terminal portion". The nucleic acid claimed does not require that the coding sequence of the carboxy terminal to encode a botulinum neurotoxin, but only is defined to comprise a nucleic acid sequence of the carboxy terminal portion. The portion selected from the carboxy terminal is any portion, and is claimed in association with other nucleic acids (a nucleic acid that comprises a nucleic acid sequence), but is required to maintain any overall coding sequence for any specific polypeptide of any specific function, therefore the "culturing" step of claim 48, is not clear as the nucleic acid of claim 39 is not required to encode a botulinum neurotoxin. Clarification, of what is expressed, and encoded in light of the claim limitations recited in claim 39, is requested.

Claims 49 recites the term "protein" and depends from claim 48 which recites the term "polypeptide". The word "protein" lacks antecedent basis in claim 48. Is the polypeptide and the insoluble protein one in the same molecule? The portion of the carboxy terminal is not claimed to be part of a protein; is the "portion" polypeptide included in a larger protein molecule? What is protein is being recovered?

Claims 53 and 54 depend from a non-elected claim. The inventions are not distinctly claimed.

Claim 53 is directed to a method of preparing an immunogenic composition. As the method only comprises a single step of culturing, the claimed methods does not correspond to the recited preamble. Is the whole recombinant host organism the immunogenic composition? The heavy chain portion is not expressed, nor isolated, nor formulated into an immunogenic composition. No preparing step of any immunogenic compositions is recited, only the host organism is cultured. The method is not distinctly claimed.

Claim 53 recites the phrase "in expressible form". What is in expressible form, the expression vector, or the carboxy-terminal portion? Both of the nucleic acid molecules recited in the claim could be in expressible form. What is in expressible form is not clear.

Claim 54 recites the phrase "recovering an insoluble protein fraction". The word protein lacks antecedent basis in the claim. What is the insoluble protein or proteins that were recovered from the organism? The protein is not defined to be the neurotoxin. What are the "organisms" insoluble proteins? No immunogenic compositions were prepared in the recited method of preparing an immunogenic composition. Clarification of the invention is requested.

Claim 85 and 86 recite the phrase "said protein" and depend from claims 82 and 39 which do not provide antecedent basis for this phrase. What is the protein? What is the host cell that would evidence the recited % of total cellular protein? What affords the recited % of total cellular protein? No structural differences are recited in the claims that define what produces the difference in the total cellular protein %.

Claim Rejections - 35 U.S.C. § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

21. Claims 39, 41, 48 and 51 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith (different inventive entity, priority date for yeast/Pichia pastoris claims is not 1993, reference provided in Applicant US-PTO 1449).

Smith discloses the claimed invention of a nucleic acid that encodes a Clostridium botulinum neurotoxin that encoded a polypeptide that has an amino acid sequence selected from SEQ ID NO 1, 3 or 5, and is capable of being expressed in a yeast, specifically Pichia pastoris. Smith discloses a recombinant Pichia pastoris host cell that encodes of a Clostridium botulinum neurotoxin (see Figure 6, legend narrative page 1546) that shares conserved coding sequences in the carboxy-terminal of the neurotoxin. A method of producing an immunogenic polypeptide is disclosed, the method comprising the steps of culturing the recombinant Pichia pastoris host cell, recovering the expressed Hc polypeptide, and purifying the polypeptide through cell extraction. An immunogenic composition was formulated and used in vaccine challenge experiments in mice (see page 1547 top of page). Smith anticipates the claimed invention.

22. Claims 39-47, 54-56, 82, 85-86 are rejected under 35 U.S.C. 102(a) as being anticipated by Halpern et al (May 1993).

Halpern et al (May 1993) disclose the claimed invention directed to a nucleic acid that comprises a nucleic acid sequence of the carboxyl terminal portion of a botulinum neurotoxin, wherein the nucleic acid encodes an amino acid sequence conserved across Clostridial neurotoxins. The disclosed nucleic acid comprises a nucleic acid sequence and encodes the amino acids "DEGWT" (see page 11189, col. 1, preparation of antibodies lines 1-2; Figure 1, and results section, that defines the nucleic acids (DNA) were capable of being expressed as they had a T7 RNA polymerase promoter and start codon added at the 5' end of the nucleic acids (see col. 2, page 11189, first paragraph; see page 11186, col. 2, experimental procedures, paragraphs 2-3).

The isolated nucleic acid encoded a synthetic polypeptide (see page 1190, col. 1, second paragraph) that was formulated into an immunogenic composition (see page 11189, col. 1, paragraph 5).

The heavy chain nucleic acid molecules that comprised the carboxyl terminal encoded polypeptides which were cloned . The recombinant mammalian host cells were *cultured* (see page 2255, col. 2, paragraph 2), the expressed (transcribed and translated) protein was then *recovered* for amino acid sequencing (see page 2258, Figure 8 and page 2258, col. 2, paragraph 1; table 3, top of page 2260; purified polypeptide, see page 11190, col. 1 first paragraph; see page 2255, col. 2, paragraph 5). The reference anticipates the instantly claimed invention.

23. Claims 39-42, 44-51, 55-56, 82, 85-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Kink et al (US Pat. 5,736,139, issue date April 7, 1998).

Kink et al disclose a nucleic acid that comprises a nucleic acid which encodes a portion of the carboxy-terminal portion of the heavy chain of botulinum neurotoxin, wherein the nucleic acid shares 100% sequence identity over 98.4 % of SEQ ID NO 1 (Kink et al SEQ ID NO 22) ,shares 99.9% sequence identity over 98.6 % of SEQ ID NO 3 (Kink et al SEQ ID NO 22), and shares

99.8 % sequence identity over 98.2 % of SEQ ID NO 5 (Kink et al SEQ ID NO 22). The nucleic acid of Kink et al is 1330 nucleotides in length, and comprises from up to 7 additional nucleic acids as compared to SEQ ID No 3 and 5. The nucleic acid of Kink et al was cloned into E.coli (see example 24, col. 110) and expressed as a polypeptide. The recombinant polypeptide was prepared by culturing

Conclusion

24. This is a non-final action.

25. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

26. Clayton MA et al, (1995, see sequence alignment provided) is cited to show a nucleic acid coding sequence for the Hc fragment of serotype A (1995).

27. Thompson et al, Eurpean Journal of Biochemistry (1990, see sequence alignment provided) is cited to show the coding sequence for type A Botulinum toxin.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

November 1, 2002

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Application No.: 09/611,419

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: additional sequences found

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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